

Effects of PRP and HA injections with intervals on pain and function in knee OA

PRP and HA on knee osteoarthritis

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Aim: The purpose of our study is to evaluate the effects of platelet-rich plasma (PRP), Hyaluronic Acid (HA), and their combination treatments on pain and functional scores in the cases of mild to moderate osteoarthritis.

Materials and Methods: One hundred twenty patients receiving PRP and/or HA injection in knee joint space were retrospectively evaluated. The mean age of the patients was 59.5± 5 years. The mean length of follow-up time was 6 months. Twenty-two patients received PRP first and after 15 days they got HA injection while 26 patients received HA first and then PRP 15 days after the first injection. Thirty-three patients were given a single dose of PRP and 39 patients were treated only with HA injection. Patients were then evaluated with WOMAC and VAS scoring systems.

Results: A statistical comparison of the groups shows that the HA+PRP group achieved significantly better clinical results. Patients receiving only HA injection had significantly worse clinical outcomes while patients receiving only PRP treatment and PRP+HA had similar results.

Discussion: In conclusion, PRP and HA combination appears to be a potentially effective treatment modality in knee osteoarthritis.

Keywords

Hyaluronic Acid; Intraarticular Injection; Knee Osteoarthritis; Platelet-Rich Plasma; Pain; WOMAC

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Introduction

Osteoarthritis is a chronic degenerative disorder characterized by joint pain, impaired mobility, and deformity [1]. The impact of osteoarthritis (OA) on society is rising due to an increase in the number of active elderly population [2]. Knee osteoarthritis decreases life quality substantially. Currently, there is no definitive non-surgical treatment for osteoarthritis and the treatment modalities that are frequently applied primarily aim at reducing pain and improving function. The first step and mainstay of therapy are usually losing weight and non-steroidal anti-inflammatory drugs (NSAIDs) [3]. Topical agents are also widely used with rather limited benefits [4]. Oral supplements including glucosamine and chondroitin sulphate are not proven to be effective and are not regarded as an ideal treatment modality in osteoarthritis [4]. Though intraarticular steroid injection in knee joint space improves pain, there could be detrimental effects on joint cartilage in the long term [5].

Intraarticular knee injections are also frequently used to reduce pain and improve function. The latest investigations have shown that intraarticular platelet-rich plasma (PRP) or Hyaluronic Acid (HA) injection in knee osteoarthritis is beneficial and does not increase the risk of septic arthritis development [6]. As described in earlier studies, HA primarily functions as supplementing viscoelastic and mechanical properties of synovial fluid and stimulating endogenous HA production from chondrocytes and synoviocytes [6]. PRP is an autologous blood product with a high number of platelets and is widely used in the orthopedic and sports medicine practice to treat bone, tendon, and ligament injuries more than over a decade, and lately, is being used to alleviating the symptoms of knee osteoarthritis as well [7]. To summarize, though various methods had been described, no single ideal non-surgical treatment modality is defined in the treatment of knee osteoarthritis.

In the current study, we compared the effect of combined PRP and HA injections with a single dose HA or PRP in the setting of mild to moderate knee osteoarthritis. Despite PRP and HA are being used in the practice of orthopedics and sports medicine for years, there are still unanswered questions regarding their clinical efficacy, and there is no consensus about how many injections with how long intervals are needed to be given to achieve best possible clinical results. A limited number of randomized studies have shown that PRP provides clinical improvement [8-10]. To our knowledge, the order of PRP and HA injections should be administered in the early-stage osteoarthritis has not been previously investigated. Therefore, the aim of this study is to compare clinical results in four groups of patients: two groups of patients receiving consecutive PRP and HA or HA and PRP injections, while the other two groups receive either a single-dose of PRP or HA treatment.

Material and Methods

One hundred twenty patients receiving intraarticular knee injection of either PRP or HA between 2018-2020 were retrospectively evaluated. Before the treatment, knee MRIs were obtained from every participant and radiological assessments were performed according to Outerbridge classification. Patients with grade 2-3 cartilage damage and knee pain more than four months were included in the study. The mean age

of the study population was 59.5 ± 4 (range 52-69). Seventy-five patients were female (% 62.5) and 45 patients were male. The mean body-mass index (BMI) was 25.9 ± 3 . Patients with a systematic disease (diabetes mellitus, rheumatologic disorders, severe cardiovascular diseases, hematologic disorders, and infections), previous lower extremity surgeries, last stage osteoarthritis, prescribed anticoagulants, and anti-aggregates, previous intraarticular injections and with missing information were excluded.

A written informed consent was obtained from all individuals participants included in the study. The study protocol was approved by the Institutional Review Board. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were followed for six months and evaluated with VAS (Visual Analogue Score) and WOMAC (Western Ontario and Mc Masters Osteoarthritis index) scores which were obtained before injections and 1, 3, and 6 months after being treated. Patients were divided into four groups as follows: 22 patients in the first group were given PRP and HA after 15 days; 26 patients in the second group were treated with HA and PRP after 15 days; 33 patients in the third group were treated with PRP, and 39 patients in the fourth group received only HA injections.

PRP Preparation

In this study, a low leukocyte ACP system was utilized which concentrates platelets while removing erythrocytes and white blood cells. Blood sample (10 ml) was drawn from the antecubital vein and centrifuged at 1500 rpm for 5 minutes, and approximately 4 ml PRP was obtained. For every patient, PRP had been prepared and injected in knee joint space in 30 minutes.

HA Prepare

Promovia 2 40 mg/ 2 ml, 1500-1600 KDalton (Pronto Pharma Care) was used in the HA group.

Statistical Analysis

Data were analyzed using a computer system with SPSS 18 pocket program. For the descriptive statistics, percentage distributions, mean \pm standard deviations were used. A mean score comparison of more than two groups was done with the Oneway Anova test with Bonferroni and Tamhane corrections. The Pearson test was used as a correlation test. $P < 0.05$ was considered statistically significant.

Results

Patients were evaluated retrospectively. Clinical scores and demographic data were obtained from patients' files. Patients were divided into 4 groups. The first group received PRP+HA, the second group was treated with HA+PRP, the third group received PRP only, and the fourth group received HA only. Table 1 shows the demographic data of the patients.

VAS scores of the 1st and 3rd months were compared between four groups. The mean score of the HA group was significantly higher than PRP+HA, HA+PRP, PRP groups while last three groups had similar results (Table 2).

VAS scores at 6 months between four groups were compared. There was no significant difference between PRP+HA and PRP groups, while the HA+PRP group had significantly lower scores and the HA group had significantly best scores (Table 2).

When four groups are compared, the 1st-month WOMAC

score of the HA+PRP group was significantly higher, while the HA+PRP and PRP groups had similar results.

The HA+PRP group had significantly higher 3rd and 6th-month WOMAC scores while the HA group had significantly lower 3rd and 6th-month WOMAC scores compared with others. Results of the PRP and PRP+HA groups were similar (Table 3).

According to correlation analysis, BMI and VAS and WOMAC scores were not significantly correlated.

Table 1. Descriptive Statistics

Group	N	Minimum	Maximum	Mean	Std. Deviation	
PRP+HA	BMI	22	22,60	44,13	26,6010	3,67588
HA+PRP	BMI	26	22,10	29,60	25,5167	1,76539
PRP	BMI	33	22,90	28,70	25,9700	1,76443
HA	BMI	39	22,60	28,60	25,8267	1,64693

Table 2. The 1st, 3rd, and 6th months VAS score comparison between groups

	Vas 1st month (mean±standart deviation)	Vas 3rd month (mean ±standart deviation)	Vas 6th month (mean ±standart deviation)	P-value
HA+PRP	6,25±0,63	5,19±0,65	3,09±0,42	0,001
PRP+HA	6,49±0,56	5,27±0,43	4,28±0,53	
PRP	6,28±0,54	5,10±0,68	4,38±0,63	
HA	7,05±0,23	5,72±0,60	5,75±0,61	

Table 3. The 1st, 3rd and 6th months WOMAC score comparison between groups

	WOMAC 1st month (mean±standart deviation)	WOMAC 3rd month (mean±standart deviation)	WOMAC 6th month (mean±standart deviation)	P-value
HA+PRP	63,36±3,28	68,62±3,01	72,37±2,18	0,001
PRP+HA	58,86±3,83	63,31±3,67	67,83±3,07	
PRP	61,19±4,42	64,01±4,18	67,73±3,80	
HA	58,78±4,99	60,33±4,56	61,89±3,99	

Discussion

The most important finding of this study is that PRP+HA combined treatment is less painful and more functional than PRP or HA treatment separately in patients with early-stage osteoarthritis. More specifically, HA injection followed by PRP treatment after fifteen days yielded the best clinical results; while PRP treatment followed by HA injection after fifteen days and single-shot PRP treatment results were similar. Nevertheless, single-dose of HA injection was found to be associated with the least clinical improvements compared with other treatment groups. In other words, the efficacy of treatment modalities is evaluated as follows: HA+PRP> PRP+HA=PRP>HA. Restrictions of our study are a low number of patients, short follow-up time, and single-dose administration of PRP and HA injections.

After being injected intraarticularly, most of the HA molecules remain in the joint space up to a few days, while the effect of the treatment usually persists for months. This fact implies that along with viscosupplementative properties, which mostly benefit the patient by lubricating the joint surfaces and thereby

mechanically decreasing friction, there are ways that HA proceeds to function through molecular modifications [11]. The current literature investigating the effects of HA at the molecular level, particularly puts emphasis on HA-CD44 receptor interaction. Apparently, this interaction yields decreased expression of a powerful proinflammatory cytokine IL-1B along with other proinflammatory molecules such as IL-6, IL-8, and TNF-A and through the decreased expression of IL-1B, HA functions to reduce the production of matrix metalloproteinase 1, 2, 3, 9 and 13 and reactive nitric oxide derivatives. Reduced PGE2, disintegrin, which is responsible for the degradation of intraarticular glycosaminoglycans and metalloproteinase with thrombospondin motifs (ADAMS) expression and heat shock protein 70 (hsp70) overexpression are also observed [11,12]. These activated pathways ultimately converge on a net chondroprotective result [13]. HA binding with TLR-2 and TLR-4 receptors eventuates decreased production of TNF-α, IL-1-β, IL-17, MMP-13 and iNOS, and interaction with ICAM-1 receptor downregulates the NF-kB pathway, in which the end product is a potent proinflammatory cytokine, IL-6. These alterations are, overall, seem to be mediating the antiinflammatory properties of HA [14].

Additionally, intraarticular HA injection also stimulates the synthesis of glycosaminoglycan and proteoglycan and mobilizes newly-synthesized macromolecules into the outer chondrocyte matrix, thereby providing protection from degradation.

Another result of HA-CD44 interaction is inactivation of matrix metalloproteinase-13, which plays a key role in subchondral bone changes during the osteoarthritis pathogenesis. There are basic science investigations suggesting that with the declined activity of MMP-13, improvement in subchondral bone density and thickness through trabecular structure alterations is seen, which eventually reduces the stress placed on articular cartilage during loading.

PRP is an autologous blood product, which is obtained from peripheral venous blood and processed into a platelet-rich suspension to be used in the treatment of bone, tendon, and ligament injuries more than over a decade. Alpha granules in the thrombocytes are known to be rich with growth factors (insulin-like growth factor-1 [IGF-1], basic fibroblast growth factor [BFGF], platelet-derived growth factor [PDGF], epidermal growth factor [EGF], vascular endothelial growth factor [VEGF], and transforming growth factor-beta [TGF-b]) upon thrombocyte stimulation. They are released to take roles in suppressing inflammation, clearing the necrotic cell debris, reconstructing the tissue, and overall, aiding in the healing process [15].

Some clinical studies and meta-analyses have shown satisfactory results obtained with HA injection while some suggest that modality is not superior to placebo [16, 17, 18]. Görmeli et al. argue that HA injection is more efficient in the setting of early-stage osteoarthritis, however its effects usually last in a time period as short as 6 months. They also claim that multiple PRP administration is associated with better clinical results than single-dose PRP or HA treatment [19]

In their randomized, double-blinded study, Patel et al. showed that when patients with early-stage knee osteoarthritis received a single-dose or double-dose PRP administration, they received better scores than patients in the control group who

were given intraarticular saline [20].

Cerza et al. reported that better results were achieved with PRP administration compared with HA injection [8].

In a study where patients were given combined PRP and HA treatment, arthralgia was shown to be mitigated, humoral and cellular immunological response was diminished and histological parameters improved compared with PRP or HA treatment alone [21].

There are studies that suggest that combined HA injection and PRP treatment provide a better option in knee osteoarthritis rather than either modality applied singularly, but to our knowledge, the effect of HA injection order and PRP treatment on the ultimate result has not been investigated so far. One of the most important results of our study is that the best clinical results are achieved by HA injection followed by a single-dose PRP treatment after fifteen days, that can be explained by the fact that introduction of HA into the joint space alters molecular pathways in a fashion that it potentializes the mechanisms of action in which PRP treatment operates. Our opinion is that this subject can and should be further elucidated with the well-designed clinical trials with a larger number of patients in terms of reproducibility of results and with the basic science investigations inquiring molecular pathways on which HA injection and PRP treatment work.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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